UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,900	11/08/2000	Moon Jong Noh	54751-015	9053

35736 7590 03/01/2007

JHK LAW
P.O. BOX 1078
LA CANADA, CA 91012-1078

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/707,900	NOH ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 6-22 have been canceled. Claims 1-5 remain pending and under consideration.

The amendment filed 12-13-06 fails to properly include the phrase "chondrocyte cells chondrocytes" in step b of claim 1 or mark the deletion of "chondrocyte cells" in step b of claim 1. The amendment filed 12-13-06 has been entered to expedite prosecution.

Priority

Examples III-VI are new in this application (pages 23-25). Example VI is not in parent application 09/702718. The effective filing date of the instant application is 11-8-00.

Information Disclosure Statement

The IDS filed 2-2-05 was considered in the office action sent 4-13-05; however, if applicants believe any of the 54 references are particularly relevant to the claimed invention, please point to such references more specifically.

Claim Rejections - 35 USC 112 - new matter

The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been withdrawn in view of the amendment.

The limitation of treating osteoarthritis with chondrocytes transfected with TGF-β1 or BMP-2 resulting in regenerating "connective tissue" has been withdrawn because the phrase "connective tissue" has been replaced with "hyaline cartilage" (claim 1).

Pg 5, lines 14-23, teaches:

"The present invention is also directed to a method of regenerating hyaline cartilage, comprising:
a) generating a recombinant viral or plasmid vector comprising a DNA sequence encoding a member of a transforming growth factor superfamily of proteins operatively linked to a promoter;
b) transfecting in vitro a population of cultured connective tissue cells with the recombinant vector, resulting in a population of transfected connective tissue cells; and
c) transplanting the transfected connective tissue cells by intraarticular injection to joint space of a mammalian host, such that expression of the DNA sequence within the joint space results in regenerating hyaline cartilage."

Pg 5, line 5 and pg 9, line 6, teach the connective tissue cells can be chondrocytes.

Pg 13, lines 1-2, teaches injecting transfected connective tissue cells into the joint to express exogenous TGF superfamily proteins in the joint space.

Pg 5, lines 11-12, teach the TGF superfamily proteins include TGF-β1 and BMP.

Page 1, lines 17-24, which states:

> "In the orthopedic field, degenerative arthritis or osteoarthritis is the most frequently encountered disease associated with cartilage damage. Almost every joint in the body, such as the knee, the hip, the shoulder, and even the wrist, is affected. The pathogenesis of this disease is the degeneration of hyaline articular cartilage (Mankin et al, J Bone Joint Surg, 52A: 460-466, 1982). The hyaline cartilage of the joint becomes deformed, fibrillated, and eventually excavated. If the degenerated cartilage could somehow be regenerated, most patients would be able to enjoy their lives without debilitating pain. There has been no method reported to date to regenerate damaged hyaline cartilage."

The limitation of "without scaffolding" in claim 1 has support on pg 12, lines 17-31, which states: "It is to be understood that while it is possible that substances such as a scaffolding or a gamework as well as various extraneous tissues may be implanted together in the gene therapy protocol of the present invention, it is preferred that such scaffolding or tissue not be included in the injection system of the invention."

Claim Rejections - 35 USC 112 - enablement

Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transfecting fibroblasts with DNA encoding TGF-β1 operably linked to a promoter, transplanting the transfected fibroblasts into a joint space of a mammal such that expression of TGF-β1 occurs resulting in generating hyaline cartilage, does not reasonably provide enablement for using chondrocytes encoding TGF-β1 or BMP-2 to treat arthritis or regenerate hyaline cartilage as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The specific combination of vector, cell and modes of delivery required to target a desired tissue and regenerate tissue *in vivo* is unpredictable. Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1).

Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art that show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

More specifically, at the time of filing Naughton taught transplanting foreskin fibroblasts to a site of cartilage damage in the presence of scaffolding and regenerating cartilage, suggested transfecting the cells with a vector encoding TGF-β1 and suggested delivering the cells intraarticularly (Naughton, claim 1; col. 10, line 58; col. 4, line 65; col. 13, line 60 - col. 16, line 33; col. 2, line 56 and col. 18, lines 8-42 which discusses administering the cells to joints that have damaged cartilage). Ikeda taught

administering a vector encoding TGF-β1 intraarticularly to obtain TGF-β1 expression (pg 1667, col. 1, third paragraph; pg 1669, col. 2). van Beuningen taught TGF-β1 administered intraarticularly generates articular cartilage (pg 307, col. 1, "intraarticular injections"; pg 308, col. 1, "stimulation of articular cartilage"). The art did not teach how to use BMP-2 to regenerate cartilage or how to use chondrocytes to regenerate cartilage.

The specification does not enable using the claimed invention to treat osteoarthritis (claim 1). Arthritis in humans causes a diverse T-cell population response against not just collagen or one antigen, but a large number of undefined antigens in the arthritic joint (Fox, July 1995, Am. J. Med., Vol. 99, pgs 82-88; pg 87, col. 1, paragraph 1; pg 84, col. 4, para. 1).

The specification taught transfecting fibroblasts with DNA encoding TGF-β1, making cartilage defects in the knees of rabbits with a knife and transplanting the transfected fibroblasts intraarticularly (pg 21, lines 19-25). Results indicated newly hyaline cartilage was formed (pg 22, lines 13-16). However, these rabbits are not art-accepted models for osteoarthritis; nor do the rabbits correlate to osteoarthritis. While arthritic joints require cartilage regeneration, removing cartilage with a knife does not reflect the complex immune response in an arthritic joint. The specification does not teach how damaging cartilage with a knife reflects the diverse T-cell response against the undefined antigens in the arthritic joint as taught by Fox (cited above). The specification does not provide adequate guidance to regenerate cartilage in an arthritic

joint because the cells administered may be attacked by the immune system and may not target the damaged area of cartilage.

The specification does not enable replacing the TGF-β1 in the examples with BMP-2 to regenerate hyaline cartilage. Nor does the specification correlate the function of TGF-β1 to BMP-2 such that cartilage could be regenerated. While the specification suggests using BMP-2 (page 11, line 9), the activities and functions of TGF-β1 and BMP-2 vary. The specification does not correlate the results obtained using TGF-β1 to BMP-2 such that hyaline cartilage would be regenerated. Nor does the specification correlate the structure or function of TGF-β1 to BMP-2 such that cartilage could be regenerated. Without such guidance, it would require one of skill undue experimentation to use BMP-2 instead of TGF-β1 to regenerate hyaline cartilage in view of the state of the art at the time of filing taken with the teachings in the specification, which are limited to transfected fibroblasts encoding TGF-β1.

The specification does not enable replacing the fibroblasts in the examples with chondrocytes to regenerate hyaline cartilage. Nor does the specification correlate the function of fibroblasts to chondrocytes such that cartilage could be regenerated. While the specification suggests using chondrocytes, the activities and functions of fibroblasts and chondrocytes vary. The specification does not correlate the results obtained using fibroblasts to chondrocytes such that hyaline cartilage would be regenerated. Nor does the specification correlate the structure or function of fibroblasts to chondrocytes such that cartilage would be regenerated. Without such guidance, it would require one of skill undue experimentation to use transfected chondrocytes instead of transfected

fibroblasts to regenerate hyaline cartilage in view of the state of the art at the time of filing taken with the teachings in the specification which are limited to transfected fibroblasts.

Given the unpredictability in the art taken with the guidance provided in the specification, it would have required one of skill undue experimentation to use chondrocytes transfected with DNA encoding TGF-β1 or BMP to regenerate hyaline cartilage or any desired connective tissue as broadly claimed.

Applicants argue the specification discusses on pg 1, lines 17-24, and injecting transfected fibroblasts into the knee (pg 21, line 20-25; pg 29, line 7); therefore, applicants' conclude applicants enable treating osteoarthritis. Applicants' argument is not persuasive. These rabbits are not art-accepted models for osteoarthritis; nor do the rabbits correlate to osteoarthritis. Removing cartilage with a knife does not reflect the complex immune response in an arthritic joint or the diverse T-cell response against the undefined antigens in the arthritic joint as taught by Fox cited above.

Applicants state the guidance presented in the specification is adequate to perform the claimed invention such that arthritis is treated. Applicants' argument is unfounded.

Applicants argue the method claimed does not require immuno-rejection. Applicants' argument is not persuasive. The model used by applicants has cartilage damaged by knife but does not model arthritis because it does not have the diverse T-cell population response against a large number of undefined antigens in the arthritic joint. Therefore, it is not readily apparent that the transfected fibroblasts used in the

examples would be able to regenerate hyaline cartilage as claimed under those conditions.

Applicants argue TGF-β1 and BMP-2 would both work in the claimed invention because they are both part of the same superfamily. Applicants' argument is not persuasive. While the specification suggests using BMP-2 (page 11, line 9), the activities and functions of TGF-β1 and BMP-2 vary. Given the unpredictability in the art, applicants have not provided adequate guidance that BMP-2 has the same growth factor activity as TGF-β1 such that hyaline cartilage is regenerated as claimed.

Applicants argue chondrocytes and fibroblasts were both able to be transfected. Therefore, applicants conclude both would work in gene therapy to regenerate hyaline cartilage as claimed. Applicants' argument is not persuasive. While the specification lists connective tissue cells as including chondrocytes, the specification does not correlate the results obtained using transfected fibroblasts to transfected chondrocytes such that cartilage would be regenerated. The structures and functions of fibroblasts and chondrocytes are materially distinct and separate. The specification does not establish chondrocytes provide the same affinity or amount of expression as fibroblasts. Therefore, the teachings in the specification do not overcome the unpredictability in the art at the time of filing regarding gene therapy for those of skill to determine that a therapeutic effect will occur if the transfected fibroblasts used on pg 21, lines 21-25, are replaced with chondrocytes as claimed.

Applicants argue the model and data provided was provided to the FDA. Applicants' argument is not persuasive. The FDA is not the Patent office and does

assess the data in the context of patent law. In this case, the model used by applicants has cartilage damaged by knife but does not model arthritis because it does not have the diverse T-cell population response against a large number of undefined antigens in the arthritic joint. Therefore, it is not readily apparent that the transfected fibroblasts used in the examples or transfected chondrocytes now claimed would regenerate hyaline cartilage under the conditions found in an arthritic joint.

Claim Rejections - 35 USC 112 - indefiniteness

Claims 2-5 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejection regarding the phrase "chondrocyte cells chondrocytes" in claim 1, b), third line, has been withdrawn because the phrase has been deleted. It is noted that the phrase was not included in its entirety with the proper markings in the amendment filed 12-13-06; however, the amendment was entered to expedite prosecution.

The rejection regarding the cells in claim 13, step b), has been withdrawn because the claim has been canceled.

Claims 2-4 are indefinite because they are dependent upon claim 13, which has been canceled. Claim 5 is included because it is dependent upon claim 4.

Double Patenting

Claims 1-5 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,797,703, application number 09/702,718. Although the conflicting claims are not

identical, they are not patentably distinct from each other because they overlap in scope. The claims of the instant application require regenerating connective tissue by transfecting chondrocytes with a viral or plasmid vector encoding TGF- beta1 or BMP and transplanting the cells by intraarticular injection into an osteoarthritic joint space of a mammal. The claims of '718 require generating hyaline cartilage by transfecting chondrocytes with a viral or plasmid vector encoding TGF- beta1 and transplanting the cells by into the joint space of a mammal. Upon review of the disclosure of '718, the claims in this application could have been claimed during prosecution of '718.

Applicants traverse the rejection without providing reasons. Applicants will consider filing a terminal disclaimer when the application is allowable. Applicants' statements are noted but fail to overcome the rejection.

Claim Rejections - 35 USC § 103

The rejection of claims 1-5 under 35 U.S.C. 103(a) as being unpatentable over Naughton (US Patent 5,842,477, Dec. 1, 1998) in view of Ikeda (Sept. 1998, J. Rheumatol., Vol. 25, pages 1666-1673) and van Beuningen (Sept. 1998, Osteoarthritis and Cartilage, Vol. 6, pages 306-317) was withdrawn because the references do not teach transplanting cells without scaffolding as newly amended (see also the final office action sent 1-24-03, pg 9).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

MGI website's "Gene Detail" and "Gene Ontology" for TGFb1.

MGI website's "Gene Detail" and "Gene Ontology" for BMP2.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER